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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)

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on _____

Signature _____

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Application Number	Filed
09/582,342	September 18, 2000
First Named Inventor	
Rudi BRANDS	
Art Unit	**Examiner**
1651	A. Ford

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.

☐ attorney or agent of record.
Registration number _____.

☒ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 **54,257**

Jennifer Leach
Signature

Jennifer Leach
Typed or printed name

202-408-4000
Telephone number

September 5, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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I. Rejection under 35 U.S.C. § 103

Claims 39-44 stand rejected under 35 U.S.C. § 103 over BRYAN GRIFFITHS & DENIS LOOBY, *Scale-Up of Suspension and Anchorage-Dependent Animal Cells, in* 75 METHODS IN MOLECULAR BIOLOGY: BASIC CELL CULTURE PROTOCOLS 59, 59-75 (Jeffrey W. Pollard & John M. Walker eds., 2d ed. 1997) ("Griffiths") in view of "Friendship Cake/Bread History" available at http://recipecircus.com and "Amish Friendship Bread" available at http://en.wikipedia.org. final Office Action, page 4.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. M.P.E.P. § 2142. In *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q. 2d 1385 (2007), the Supreme Court confirmed that the "framework for applying the statutory language of §103" was still based on its landmark decision in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Although the question of obviousness must be resolved on the basis the *Graham* factors, the Supreme Court pointed out that there is no inconsistency between the *Graham* analysis and the idea underlying the teaching, suggestion, or motivation ("TSM") test. *KSR*, 127 S. Ct. at 1741, 82 U.S.P.Q. 2d at 1389. Further, in its recent published examination guidelines, the USPTO solidified that the TSM test is a valid rationale for determining obviousness. *See* M.P.E.P. § 2141.

In the present § 103 rejection, the Examiner is relying on the TSM rationale to support her conclusion of obviousness. *See* final Office Action at pages 5-7. Under this rationale, the Examiner must at least demonstrate (1) a finding that there is some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available of ordinary skill in the art, to modify the reference or to combine reference teachings; and (2) a finding that there was a reasonable expectation of success; to make the proposed modification. *See* M.P.E.P. § 2143(G). Applicant respectfully submits that neither of these findings can be made, and thus, the Examiner has failed to establish a *prima facie* case of obviousness.

First, Applicant points out that at page 5 of the final Office Action the Examiner incorrectly asserts that Griffiths discloses "splitting and passaging the cells of their 'preproduction batch.'" *See*

pages 65-67 and Fig. 4. A thorough review of Griffiths reveals no discussion of splitting cells into two parts in the manner claimed. When it comes to growing cells, the cells in Griffiths are always used as a single "part" and are never diverted for more than one purpose. Moreover, the Examiner's handwritten note on page 67 of Griffiths identifies step 6 of the procedure disclosed as a "discontinuous procedure." This is also incorrect. The separation of cells from their substrate after a period of growth is not a repeated discontinuous process which includes "splitting" of anchorage-dependent cells, as defined in Applicant's claimed invention. *See* page 3, lines 12-18 of Applicant's specification.

On page 5 of the final Office Action, the Examiner also acknowledges that Griffiths does not teach or suggest a "repeated discontinuous process," as in Applicant's claimed invention. However, the Examiner asserts that the claimed repeated discontinuous (splitting) process would have been obvious based on the disclosure in articles titled "Friendship Cake/Bread History" and "Amish Friendship Bread." *See* final Office Action at page 5. Applicant respectfully disagrees with the Examiner's assertion for at least the following reasons.

The primary reference cited in the § 103 rejection, Griffiths, discloses protocols for preparing cell cultures. To the contrary, the secondary references, the "Friendship Cake/Bread History" and the "Amish Friendship Bread" articles only disclose a process of preparing bread. Applying the Graham factors, and considering the level of ordinary skill in the area of cell culture protocols, one would not conclude that this level includes the skill of a baker. Therefore, there is no reason why one skilled in that particular art would consider applying techniques used in making bread to a process for preparing cells for the production of a biological, for example, a virus. Moreover, even though the "Friendship Cake/Bread History" and the "Amish Friendship Bread" articles may disclose dividing up the starter culture into two parts, given that the process of making bread is completely unrelated to cell culture protocols, there is no way one of ordinary skill in the art would have been able to predict the results of using this technique in a scale-up process for the production a biological with any reasonable expectation of success, and without the benefit of hindsight.

Further, there are technical difficulties, e.g., homogeneity problems, associated with scaling-up anchorage-dependent cells. Indeed, Griffiths even recognizes these difficulties. *See* pages 59-60 and 65-66. Because of these difficulties, other references in the pertinent art, for example WO 97/37000 to Gröner et al. ("Gröner") (submitted with the IDS filed May 7, 2008), teach away from scale-up of anchorage anchorage-dependent (adherent) cells for use in the production of a biological. In particular, at page 3, line 18 to page 4, lines 16, Gröner discusses the problems associated with scaling up of anchorage-dependent cells. To address these problems, the process in Gröner converts anchorage-dependent cells to cells that grow in suspension. *See* claim 1, page 4, lines 19-24, page 5, lines 18-26, and Example 1.

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is "strong evidence of unobviousness." *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986). Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52, 148 U.S.P.Q. 479, 484 (1984). As discussed above, Gröner discourages scaling-up of anchorage-dependent cell systems for the production of a biological. Considering the drawbacks associated with scaling up anchorage-dependent cells, it would be unlikely for one of ordinary skill in the art to use anchorage-dependent cells when devising a scaled-up preparation of cells for use in the production of biologicals, and one of ordinary skill would not have done so with any reasonable expectation of success.

In view of the foregoing, Applicant submits that the Examiner has failed to establish that the claimed invention is *prima facie* obvious in view of the cited art. However, even if the Examiner has established a *prima facie* case of obviousness, which she has not, Applicant can come forward with arguments and/or evidence to rebut the *prima facie* case. *See* M.P.E.P. § 2145. Rebuttal evidence may include evidence of "secondary considerations," such as long felt but unsolved needs. *See id.*; *see also Graham v. John Deere Co.*, 383 U.S. at 17, 148 U.S.P.Q. at 467.

The production of biologicals on cell lines requires the preparation of large amounts of cells using a scaling up procedure in bioreactors. Typically, continuous processes are used for scaling up a cell culture population in the context of producing a biological. *See* Applicant's specification at page 3, lines 20-23. First, cells are grown in a first bioreactor, and after a certain cell density is reached, the cells are fed continuously from the first bioreactor into a second bioreactor. *Id.* at lines 24-25. In this second bioreactor, viruses are grown on the cells and subsequently these viruses are withdrawn continuously from this second bioreactor. *Id.* at lines 25-27. Generally, these types of preparation procedures are very time consuming and necessitate the operation of a large number of bioreactors for the preparation of the cells as well as for the production of the biologicals. *See id.* at page 1, lines 29-32. Thus, there has been a long-felt need for a faster and more efficient process.

Applicant has met this need by inventing a new and faster process for scaling up a cell culture for the production of a biological, wherein the cells are anchorage dependent cells. Unlike continuous scaling up procedures, Applicant's claimed method uses a discontinuous process. *See* Applicant's specification at page 2, lines 1-15. In embodiments of the claimed invention, cells are cultured to produce a preproduction batch, and then the cells of the preproduction batch are divided into two parts. *See id.* at page 2, lines 1-15. The first part, approximately 80-90% of the cells, is used to prepare a culture of cells to grow a biological such as a virus for a vaccine. *Id.* at page 2, lines 4-5 and 27-28. The second part, approximately 10-20% of the preproduction batch, is used as a seed for at least one additional batch not immediately used for the production of any biological product. *See id.* at page 2, lines 6-7 and 30-32. The cells of the second part of the preproduction batch can be expanded to a greater cell population for the preparation of at least one subsequent preproduction batch. *See e.g., id.* at page 6, lines 15-16. Thus, using Applicant's claimed method, a vaccine manufacturer, for example, can rapidly produce vaccine without waiting for all preproduction batches to reach full maturity. *See* Applicant's specification at page 3, line 35 to page 4, line 2.

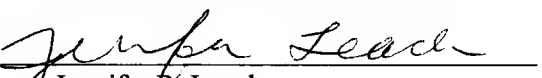
As discussed above, the Examiner asserts that the claimed repeated discontinuous (splitting) process would have been obvious based on the disclosure in articles titled "Friendship Cake/Bread History" and "Amish Friendship Bread." *See* final Office Action at page 5. However, the fact of the matter is, prior to Applicant's claimed invention no one considered splitting the preproduction batch (starter culture) used in the production of a biological into two parts. Prior to Applicant's claimed invention, cells for use in the production of a biological were only produced using a continuous process in which the entire preproduction batch was used for preparing a biological. As discussed above, this continuous process was slow and necessitated a number of bioreactors for the preparation of cells as well as for the production of the biological. Recognizing this long-felt need in the industry, Applicant invented a method for the preparation of cells for use in the production of a biological comprising a discontinuous process in which the preproduction batch was divided into two parts: a first part used for the production of a biological and a second part used as a seed for the preparation of at least one subsequent preproduction batch. By splitting the preproduction batch into two parts, Applicant's claimed method provides a faster and more efficient process for scaling up a cell culture for the production of a biological. Thus, Applicant's claimed method satisfied a long-felt, but unsolved need in the industry, which is further evidence that rebuts any *prima facie* case of obviousness based on the cited references.

In view of the above, Applicant respectfully requests reconsideration and withdrawal of the § 103 rejection.

Please grant any extensions of time and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 5, 2008

By: 
Jennifer R. Leach
Reg. No. 54,257